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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicants : Guy W. Bemis et al.
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For : INHIBITORS OF INTERLEUKIN-1 β CONVERTING
ENZYME

New York, New York
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Hon. Commissioner for Patents
P.O. Box 2327
Arlington, VA 22202

INFORMATION DISCLOSURE STATEMENT

Sir:

Pursuant to 37 C.F.R. §§ 1.56 and 1.97, applicants, through their attorney
or agent, make of record the documents listed below.

United States Patents

<u>Inventor</u>	<u>Serial No.</u>	<u>Date</u>
Jones et al.	4,276,298	June 30, 1981
Jones et al.	4,369,183	January 18, 1983
Mueller et al.	4,499,295	February 12, 1985
Mueller et al.	4,551,279	November 5, 1985
Mueller et al.	4,584,397	April 22, 1986
Dower et al.	4,968,607	November 6, 1990
Digenis et al.	5,008,245	April 16, 1991
Krantz et al.	5,055,451	October 8, 1991
Dower et al.	5,081,228	January 14, 1992
Krantz et al.	5,158,936	October 27, 1992
Dower et al.	5,180,812	January 19, 1993
Zimmerman et al.	5,374,623	December 20, 1994
Bills et al.	5,411,985	May 2, 1995
Black et al.	5,416,013	May 16, 1995
Chapman et al.	5,430,128	July 4, 1995
Chapman et al.	5,434,248	July 18, 1995
Dolle et al.	5,462,939	October 31, 1995
Zimmerman et al.	5,486,623	January 23, 1996
Mallamo et al.	5,498,616	March 12, 1996
Daumy et al.	5,498,695	March 12, 1996

Dolle et al.	5,552,400	September 3, 1996
Dolle et al.	5,565,430	October 15, 1996
Dolle et al.	5,585,357	December 17, 1996
Dolle et al.	5,585,486	December 17, 1996
Dolle et al.	5,639,745	June 17, 1997
Dolle et al.	5,670,494	September 23, 1997

PCT Patent Applications

WO 91/15577 (published October 17, 1991)

WO 93/05071 (published March 18, 1993)

WO 93/09135 (published May 13, 1993)

WO 93/14777 (published August 5, 1993)

WO 93/16710 (published September 2, 1993)

WO 93/25683 (published December 23, 1993)

WO 93/25685 (published December 23, 1993)

WO 93/25694 (published December 23, 1993)

WO 94/00154 (published January 6, 1994)

WO 95/00160 (published January 5, 1995)

WO 95/05192 (published February 23, 1995)

WO 94/03480 (published February 17, 1994)

European Patent Applications

EP-A-0 275 101 (published July 20, 1988)

EP-A-0 410 411 (published January 30, 1991)

EP-A-0 417 721 (published March 20, 1991)
EP-A-0 479 489 (published April 8, 1992)
EP-A-0 504 938 (published September 23, 1992)
EP-A-0 519 748 (published December 23, 1992)
EP-A-0 525 420 (published February 3, 1993)
EP-A-0 528 487 (published February 24, 1993)
EP-A-0 529 713 (published March 3, 1993)
EP-A-0 533 226 (published March 24, 1993)
EP-A-0 547 699 (published June 6, 1993)
EP-A-0 618 223 (published October 5, 1994)
EP-A-0 623 592 (published November 9, 1994)
EP-A-0 623 606 (published November 9, 1994)
EP-A-0 628 550 (published December 14, 1994)
EP-A-0 644 198 (published March 22, 1995)
EP-A-0 533 350 (published March 24, 1993)

Other Patent Documents

AU-A-64514/94 (published December 8, 1994)

Articles

D. Alberg & S. Schreiber, "Structure-Based Design of a Cyclophilin-Calcineurin Bridging Ligand", Science, 262, pp. 248-250 (1993).

P. Andrews, "Functional Groups, Drug-Receptor Interactions and Drug Design", Trends Pharmacol. Sci., 7, pp. 148-151 (1986).

- K. Appelt et al., "Design of Enzyme Inhibitors Using Iterative Protein Crystallographic Analysis", J. Med. Chem., 34, pp. 1925-1934 (1991).
- M. Ator, "Peptide and Non-peptide Inhibitors of Interleukin-1 β Converting Enzyme", Cambridge Healthtech Institute (Inflammatory Cytokine Antagonists Targets, Strategies, and Indication), (1994).
- M.A. Ator and R. E. Dolle, "Interleukin-1 β Converting Enzyme: Biology and the Chemistry of Inhibitors", Curr. Pharm. Design, 1, pp. 191-210 (1995).
- E. Baker & J. Drenth, "The Thiol Proteases: Structure and Mechanism", in Biological Macromolecules and Assemblies, 3, pp. 313-368 (F. Jurnak & A. McPherson eds., 1987).
- J. Baldwin et al., "Thienothiopyran-2-sulfonamides: Novel Topically Active Carbonic Anhydrase Inhibitors for the Treatment of Glaucoma", J. Med. Chem., 32, pp. 2510-2513 (1989).
- M. Barinaga, "Death Gives Birth to the Nervous System. But How?", Science, 259, pp. 762-763 (1993).
- P. Bartlett et al., "Caveat: A Program to Facilitate the Structure-derived Design of Biologically Active Molecules", Molecular Recognition: Chemical and Biochemical Problems, 78, pp. 182-196 (1989).
- P. Bender & J. Lee, "Pharmacological Modulation of Interleukin-1", Annu. Rep. Med. Chem., 25, pp. 185-193 (1989).
- R. Black et al., "Activation of Interleukin-1 β by a Co-induced Protease", FEBS Lett, 247, pp. 386-390 (1989).
- H. Böhm, "The Computer Program LUDI: A New Method for the De Novo Design of Enzyme Inhibitors", J. Comput. Aided Mol. Des., 6, pp. 61-78 (1992).
- J. Breitner et al., "Inverse Association of Anti-inflammatory Treatments and Alzheimer's Disease: Initial Results of a Co-twin Control Study", Neurology, 44, pp. 227-232 (1994).
- B. Brooks et al., "CHARMM: A Program for Macromolecular Energy, Minimization, and Dynamics Calculations", J. Comput. Chem., 4, pp. 187-217 (1983).
- A. Brünger, "Extension of Molecular Replacement: A New Search Strategy Based on Patterson Correlation Refinement", Acta Crystallogr. A, 46, pp. 46-57 (1990).

- A. Brünger & A. Krukowski, "Slow-Cooling Protocols for Crystallographic Refinement by Simulated Annealing", Acta Crystallogr. A, 46, pp. 585-593 (1990).
- U. Burkett & N. Allinger, "Methods for the Computation of Molecular Geometry" in Molecular Mechanics, pp. 59-78 (1982).
- M. Carson, "Ribbons 2.0", J. App. Crystallogr., 24, pp. 958-961 (1991).
- F. Casano et al., "The Structure and Complete Nucleotide Sequence of the Murine Gene Encoding Interleukin-1 β Converting Enzyme (ICE)", Genomics, 20, pp. 474-481 (1994).
- D. Cerretti et al., "Molecular Cloning of the Interleukin-1 β Converting Enzyme", Science, 256, pp. 97-100 (1992).
- K. Chapman, "Synthesis of a Potent, Reversible Inhibitor of Interleukin-1 β Converting Enzyme", Bioorg. Med. Chem. Lett., 2, pp. 613-618 (1992).
- N. Cohen, "Drug Design in Three Dimensions", Advances in Drug Research, 14, pp. 41-145 (1985).
- N. Cohen, "Rational Drug Design and Molecular Modeling", Drugs of the Future, 10, pp. 311-328 (1985).
- N. Cohen et al., "Molecular Modeling Software and Methods for Medicinal Chemistry", J. Med. Chem., 33, pp. 883-894 (1990).
- D. Davies & D. Segal, "Protein Crystallization: Micro Techniques Involving Vapor Diffusion", Methods Enzymol., 22, pp. 266-269 (1971).
- K. Dill, "Dominant Forces in Protein Folding", Biochemistry, 29, pp. 7133-7155 (1990).
- C. Dinarello, "Role of Interleukin-1 in Infectious Diseases", Immunol. Rev., 127, pp. 119-146 (1992).
- C. Dinarello et al., "Anticytokine Strategies in the Treatment of the Systemic Inflammatory Response Syndrome", J. Am. Med. Assoc., 269, pp. 1829-1835 (1993).
- R. Dolle et al., "Aspartyl α -((Diphenylphosphinyl)oxy)methyl Ketones as Novel Inhibitors of Interleukin-1 β Converting Enzyme. Utility of the Diphenylphosphinic Acid Leaving Group for the Inhibition of Cysteine Proteases", J. Med. Chem., 38, pp. 220-222 (1995).

- R. Dolle et al., "Aspartyl α -((1-Phenyl-3-(trifluoromethyl)-pyrazol-5-yl)oxy)methyl Ketones as Interleukin-1 β Converting Enzyme Inhibitors. Significance of the P₁ and P₃ Amido Nitrogens for Enzyme-Peptide Inhibitor Binding", J. Med. Chem., 37, pp. 3863-3865 (1994).
- R. Dolle et al., "P₁ Aspartate-Based Peptide α -((2,6-Dichlorobenzoyl)oxy)methyl Ketones as Potent Time-Dependent Inhibitors of Interleukin-1 β -Converting Enzyme" J. Med. Chem., 37, pp. 563-564 (1994)
- S. Ealick et al., "Application of Crystallographic and Modeling Methods in the Design of Purine Nucleoside Phosphorylase Inhibitors", Proc. Natl. Acad. Sci. USA, 88, pp. 11540-11544 (1991).
- P. Edwards et al., "Design, Synthesis, and Kinetic Evaluation of a Unique Class of Elastase Inhibitors, the Peptidyl α -Ketobenzoxazoles, and the X-ray Crystal Structure of the Covalent Complex between Porcine Pancreatic Elastase and Ac-Ala-Pro-Val-2-Benzoxazole", J. Am. Chem. Soc., 114, pp. 1854-1863 (1992).
- H. Eklund et al., "Three-dimensional Structure of Horse Liver Alcohol Dehydrogenase at 2.4 Å Resolution", J. Mol. Biol., 102, pp. 27-59 (1976).
- P.R. Elford et al., "Reduction of Inflammation and Pyrexia in the Rat by Oral Administration of SDZ 224-015, an Inhibitor of the Interleukin-1 β Converting Enzyme", British Journal of Pharmacology, 115, pp. 601-606 (1995).
- J. Erickson et al., "Design, Activity, and 2.8 Å Crystal Structure of a C₂ Symmetric Inhibitor Complexed to HIV-1 Protease", Science, 249, pp. 527-533 (1990).
- T. -P.D. Fan et al., "Stimulation of Angiogenesis by Substance P and Interleukin-1 in the Rat and Its Inhibition by NK₁ or Interleukin-1 Receptor Antagonists", Br. J. Pharmacol., 110, 43-49 (1993).
- I. Fauszt et al., "Inhibition of Interleukin-1 β Converting Enzyme by Peptide Derivatives", Proc. of the 13th Am. Peptide Symp., June 20-25, 1993; Hodges, R.S. and Smith, J.A., Eds., Peptides, pp. 589-591 (1994).
- D.S. Fletcher et al., "A Synthetic Inhibitor of Interleukin-1 β Converting Enzyme Prevents Endotoxin-Induced Interleukin-1 β Production In Vitro and In Vivo", J. Interfer. Cytokine Res., 15, pp. 243-248 (1995).
- V. Gagliardini et al., "Prevention of Vertebrate Neuronal Death by the crmA Gene", Science, 263, pp. 826-828 (1994).

T. Geiger et al., "Neutralization of Interleukin-1 β Activity in vivo with a Monoclonal Antibody Alleviates Collagen-induced Arthritis in DBA/1 Mice and Prevents the Associated Acute-phase Response", Clin. Exp. Rheumatol., 11, pp. 515-522 (1993).

A. Giannis & T. Kolter, "Peptidomimetics for Receptor Ligands-Discovery, Development, and Medical Perspectives", Angew. Chem. Int. Ed. Engl. 32, pp. 1244-1267 (1993).

P. Goodford, "A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules", J. Med. Chem., 28, pp. 849-857 (1985).

D. Goodsell & A. Olson, "Automated Docking of Substrates to Proteins by Simulated Annealing", Proteins: Structure, Function, and Genetics, 8, pp. 195-202 (1990).

T. Graybill et al., "The Preparation and Evaluation of Peptidic Aspartyl Hemiacetals as Reversible Inhibitors of ICE", Am. Chem. Soc. Abs. (206th Natl. Mtg.), MEDI 235 (1993).

T. Graybill, et al., "Preparation and Evaluation of Peptidic Aspartyl Hemiacetals as Reversible Inhibitors of Interleukin-1 β Converting Enzyme (ICE)", Int. J. Peptide Protein Res., 44, pp. 173-182 (1994).

W. Griffin et al., "Brain Interleukin 1 and S-100 Immunoreactivity are Elevated in Down Syndrome and Alzheimer Disease", Proc. Natl. Acad. Sci. USA, 86, pp. 7611-7615 (1989).

C. Hammerberg et al., "Interleukin-1 Receptor Antagonist in Normal and Psoriatic Epidermis", J. Clin. Invest., 90, pp. 571-583 (1992).

S. Hanessian et al., "Design and Synthesis of a Prototype Model Antagonist of Tachykinin NK-2 Receptor", Bioorg. Med. Chem. Lett., 11, 1397-1400 (1994).

E. Harris, "Rheumatoid Arthritis: Pathophysiology and Implications for Therapy", N. Eng. J. Med., 322, pp. 1277-1289 (1990).

W. Hendrickson et al., "Selenomethionyl Proteins Produced for Analysis by Multiwavelength Anomalous Diffraction (MAD): A Vehicle for Direct Determination of Three-dimensional Structure", EMBO J., 9, pp. 1665-1672 (1990).

R. Hirschmann et al., "The First Design and Synthesis of a Steroidal Peptidomimetic. The Potential Value of Peptidomimetics in Elucidating the Bioactive Conformation of Peptide Ligands", J. Am. Chem. Soc., 114, pp. 9699-9701 (1992).

- R. Hirschmann et al., "Nonpeptidal Peptidomimetics with a β -D-Glucose Scaffolding. A Partial Somatostatin Agonist Bearing a Close Structural Relationship to a Potent, Selective Substance P Antagonist", J. Am. Chem. Soc., 114, pp. 9217-9218 (1992).
- A. Holmgren et al., "Three-dimensional Structure of Escherichia coli Thioredoxin-S₂ to 2.8Å Resolution", Proc. Natl. Acad. Sci. USA, 72, pp. 2305-2309 (1975).
- A. Hopfinger, "Computer-Assisted Drug Design", J. Med. Chem., 28, pp. 1133-1139 (1985)
- A. Hopfinger & B. Burke, "Molecular Shape Analysis: A Formalism to Quantitatively Establish Spatial Molecular Similarity", in Concepts and Applications of Molecular Similarity, pp. 173-209 (M. Johnson & G. Maggiora eds., 1990).
- A. Howard et al., "High-Level Production and Characterization of Functional Human Interleukin-1 β Converting Enzyme in Baculovirus and E.coli Expression Systems", J. Cell. Biochem. Suppl., 17B, p. 146 (1993).
- A. Howard et al., "Human Interleukin-1 β Converting Enzyme: A Mutational Analysis of Proenzyme Activation", J. Cell. Biochem. Suppl., 17B, p. 113 (1993).
- A. Howard et al., "IL-1-Converting Enzyme Requires Aspartic Acid Residues for Processing of the IL-1 β Precursor at Two Distinct Sites and Does Not Cleave 31-kDa IL-1 α ", J. Immunol., 147, pp. 2964-2969 (1991).
- I. Kamphuis et al., "Thiol Proteases: Comparative Studies Based on the High-resolution Structures of Papain and Actinidin, and on Amino Acid Sequence Information for Cathepsins B and H, and Stem Bromelain", J. Mol. Biol., 182, pp. 317-329 (1985).
- J. Knowles, "Tinkering with Enzymes: What are We Learning?", Science, 236, pp. 1252-1258 (1987).
- M. Kostura et al., "Identification of a Monocyte Specific Pre-Interleukin 1 β Convertase Activity", Proc. Natl. Acad. Sci. USA, 86, pp. 5227-5231 (1989).
- K. Kuida et al., "Altered Cytokine Export and Apoptosis in Mice Deficient in Interleukin-1 β Converting Enzyme", Science, 267, pp. 2000-2003 (1995)
- I. Kuntz et al., "A Geometric Approach to Macromolecule-Ligand Interactions", J. Mol. Biol., 161, pp. 269-288 (1982).
- E. Lattman, "Use of the Rotation and Translation Functions", Methods Enzymol., 115, pp. 55-77 (1985).

- P. Li et al., "Mice Deficient in IL-1 β -Converting Enzyme are Defective in Production of Mature IL-1 β and Resistant to Endotoxic Shock", Cell, 80, pp. 401-411 (1995).
- C. Lipinski, "Bioisosterism in Drug Design", Annu. Rep. Med. Chem., 21, pp. 283-291 (1986).
- G. Lonnemann et al., "Differences in the Synthesis and Kinetics of Release of Interleukin 1 α , Interleukin 1 β and Tumor Necrosis Factor from Human Mononuclear Cells", Eur. J. Immunol., 19, pp. 1531-1536 (1989).
- A. MacKenzie et al., "An Inhibitor of the Interleukin-1 β -Processing Enzyme Blocks IL-1 Release and Reduces Pyrexia and Acute Inflammation", Inflammation Research Association (7th Internat. Conf.), W42 (1994)
- T. Mandrup-Poulsen et al., "Involvement of Interleukin 1 and Interleukin 1 Antagonist in Pancreatic β -Cell Destruction in Insulin-dependent Diabetes Mellitus", Cytokine, 5, pp. 185-191 (1993).
- C. March et al., "Cloning, Sequence and Expression of Two Distinct Human Interleukin-1 Complementary DNAs", Nature, 315, pp. 641-647 (1985).
- G. Marshall, "Computer-Aided Drug Design", Annu. Rev. Pharmacol. Toxicol., 27, pp. 193-213 (1987).
- G. Marshall & I. Motoc, "Approaches to the Conformation of the Drug Bound to the Receptor", Molecular Graphics and Drug Design, pp. 115-156 (A. Burgen et al. eds., 1986).
- Y. Martin, "3D Database Searching in Drug Design", J. Med. Chem., 35, pp. 2145-2154 (1992).
- J. Marx, "Cell Death Studies Yield Cancer Clues", Science, 259, pp. 760-761 (1993).
- D. Mayer et al., "A Unique Geometry of the Active Site of Angiotensin-Converting Enzyme Consistent with Structure-Activity Studies", J. Comput. Aided Mol. Des., 1, pp. 3-16 (1987).
- R. Ménard et al., "Contribution of the Glutamine 19 Side Chain to Transition-State Stabilization in the Oxyanion Hole of Papain", Biochemistry, 30, pp. 8924-8928 (1991).
- R. Ménard et al., "Importance of Hydrogen-Bonding Interactions Involving the Side Chain of Asp 158 in the Catalytic Mechanism of Papain", Biochemistry, 30, pp. 5531-5538 (1991).

- E. Meng et al., "Automated Docking with Grid-Based Energy Evaluation", J. Comput. Chem., 13, pp. 505-524 (1992).
- B. Miller et al., "Inhibition of Mature IL-1 β Production in Murine Macrophages and a Murine Model of Inflammation by WIN 67694, an Inhibitor of IL-1 β Converting Enzyme¹", J. Immunol., 154, pp. 1331-1338 (1995).
- D. Miller et al., "The IL-1 β Converting Enzyme as a Therapeutic Target", Ann. N.Y. Acad. Sci., 696, pp. 133-148 (1993).
- S. Miller et al., "The Accessible Surface Area and Stability of Oligomeric Proteins", Nature, 328, pp. 834-836 (1987).
- A. Miranker & M. Karplus, "Functionality Maps of Binding Sites: A Multiple Copy Simultaneous Search Method", Proteins: Structure, Function, and Genetics, 11, pp. 29-34 (1991).
- M. Miura et al., "Induction of Apoptosis in Fibroblasts by IL-1 β -Converting Enzyme, a Mammalian Homolog of the C. elegans Cell Death Gene ced-3", Cell, 75, pp. 653-660 (1993).
- A.M.M. Mjalli et al., "Activated Ketones as Potent Reversible Inhibitors of Interleukin-1 β Converting Enzyme", Bioorg. Med. Chem. Lett., 4, pp. 1965-1968 (1994).
- A.M.M. Mjalli et al., "Phenylalkyl Ketones as Potent Reversible Inhibitors of Interleukin-1 β Converting Enzyme", Bioorg. Med. Chem. Lett., 3, pp. 2689-2692 (1993).
- S. Molineaux et al., "Interleukin 1 β (IL-1 β) Processing in Murine Macrophages Requires a Structurally Conserved Homologue of Human IL-1 β Converting Enzyme", Proc. Natl. Acad. Sci. USA, 90, pp. 1809-1813 (1993).
- B. Mosley et al., "Determination of the Minimum Polypeptide Lengths of the Functionally Active Sites of Human Interleukins 1 α and 1 β ", Proc. Natl. Acad. Sci. USA, 84, pp. 4572-4576 (1987).
- M.D. Mullican et al., "The Synthesis and Evaluation of Peptidyl Aspartyl Aldehydes as Inhibitors of ICE", Bioorg. Med. Chem. Lett., 4, 2359-2364 (1994).
- C.M. Nalin, "Apoptosis Research Enters the ICE Age", Structure, 3, pp. 143-145 (1995).
- M. Navia & M. Murcko, "Use of Structural Information in Drug Design", Curr. Opin. Struc. Biol., 2, pp. 202-210 (1992).

- M. Nett et al., "Molecular Cloning of the Murine IL-1 β Converting Enzyme cDNA", J. Immunol., 149, pp. 3254-3259 (1992).
- M. Nett-Fiordalisi et al., "Characterization and Activation of the Murine Interleukin-1 β (IL-1 β Converting Enzyme)", J.Cell. Biochem. Suppl., 17B, p. 117 (1993).
- Y. Nishibata & A. Itai, "Automatic Creation of Drug Candidate Structures Based on Receptor Structure. Starting Point for Artificial Lead Generation", Tetrahedron, 47, pp. 8985-8990 (1991).
- C. Noren et al., "A General Method for Site-Specific Incorporation of Unnatural Amino Acids into Proteins", Science, 244, pp. 182-188 (1989).
- I. Noronha et al., "In situ Production of TNF- α , IL-1 β and IL-2R in ANCA-positive Glomerulonephritis", Kidney Int., 43, pp. 682-692 (1993).
- K. Ohlsson et al., "Interleukin-1 Receptor Antagonist Reduces Mortality from Endotoxin Shock", Nature, 348, pp. 550-552 (1990).
- J. Oppenheim et al., "There is More than One Interleukin 1", Immunol. Today, 7, pp. 45-55 (1986).
- M. Pennington & N. Thornberry, "Synthesis of a Fluorogenic Interleukin-1 β Converting Enzyme Substrate Based on Resonance Energy Transfer", Pept. Res., 7, pp. 72-76 (1994).
- R. Peters & R. McKinstry, "Three-Dimensional Modeling and Drug Development: Has "Rational" Drug Design Arrived?" Biotechnology (N Y), 12, pp. 147-150 (1994).
- J. Plattner & D. Norbeck, "Obstacles to Drug Development from Peptide Leads", in Drug Discovery Technologies, pp. 92-126 (C. Clark & W. Moss eds., 1990).
- L. Polgár, "On the Mode of Activation of the Catalytically Essential Sulfhydryl Group of Papain", Eur. J. Biochem., 33, pp. 104-109 (1973).
- C. Prasad et al., "P_i Aspartate-Based Peptide α -Arylacyloxy- and α -Aryloxymethyl Ketones as Potent Time-Dependent Inhibitors of Interleukin 1 β Converting Enzyme", Am. Chem. Soc. Abs. (24th Med. Chem. Symp.), 66 (1994).
- C. Ray et al., "Viral Inhibition of Inflammation: Cowpox Virus Encodes an Inhibitor of the Interleukin-1 β Converting Enzyme", Cell, 69, pp. 597-604 (1992).

- L. Reiter, "Peptidic p-Nitroanilide Substrates of Interleukin-1 β -Converting Enzyme", Int. J. Pept. Protein Res., 43, pp. 87-96 (1994).
- L. Revesz et al., "Synthesis of P1 Aspartate-Based Peptide Acyloxymethyl and Fluoromethyl Ketones as Inhibitors of Interleukin-1 β -Converting Enzyme", Tetrahedron Lett., 35, pp. 9693-9696 (1994).
- C. Ring et al., "Structure-based Inhibitor Design by Using Protein Models for the Development of Antiparasitic Agents", Proc. Natl. Acad. Sci. USA, 90, pp. 3583-3587 (1993).
- R.P. Robinson and K.M. Donahue, "Synthesis of a Peptidyl Difluoro Ketone Bearing the Aspartic Acid Side Chain: An Inhibitor of Interleukin-1 β Converting Enzyme", J. Org. Chem., 57, 7309-7314 (1992).
- M.J. Salvatore et al., "L-741,494, A Fungal Metabolite that is an Inhibitor of Interleukin-1 β Converting Enzyme", J. Nat. Prods., 57, 755-760 (1994).
- J. Sandberg et al., "Treatment with an Interleukin-1 Receptor Antagonist Protein Prolongs Mouse Islet Allograft Survival", Diabetes, 42, pp. 1845-1851 (1993).
- I. Schechter & A. Berger, "On the Size of the Active Site in Proteases. I. Papain", Biochem. Biophys. Res. Commun., 27, pp. 157-162 (1967).
- S. Schmidt et al., "Synthesis and Evaluation of Aspartyl α -Chloro-, α -Aryloxy-, and α -Arylacyloxymethyl Ketones as Inhibitors of Interleukin-1 β Converting Enzyme", Am. Chem. Soc. Abs. (208th Natl. Mtg.), MEDI 4, (1994).
- B. Shivers et al., "Molecular Cloning of Rat Interleukin-1 β -Converting Enzyme: Distribution and Regulation", J. Cell. Biochem. Suppl., 17B, p. 119 (1993).
- I. Singer et al., "Interleukin 1 β is Localized in the Cytoplasmic Ground Substance but is Largely Absent from the Golgi Apparatus and Plasma Membranes of Stimulated Human Monocytes", J. Exp. Med., 167, pp. 389-407 (1988).
- P. Sleath et al., "Substrate Specificity of the Protease that Processes Human Interleukin-1 β ", J. Biol. Chem., 265, pp. 14526-14528 (1990).
- A.F. Spatola, in "Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins", 7, ch. 5, pp. 267-281, Weinstein, B., ed., Marcel Dekker, Inc., New York (1983).

- R. Taylor & O. Kennard, "Hydrogen-Bond Geometry in Organic Crystals", Acc. Chem. Res., 17, pp. 320-326 (1984).
- C. Thornber, "Isosterism and Molecular Modification in Drug Design", Chem. Soc. Rev., 8, pp. 563-580 (1979).
- N. Thornberry et al., "A Novel Heterodimeric Cysteine Protease is Required for Interleukin-1 β Processing in Monocytes", Nature, 356, pp. 768-774 (1992).
- N. Thornberry et al., "Inactivation of Interleukin-1 β Converting Enzyme by Peptide (Acyloxy)methyl Ketones", Biochemistry, 33, pp. 3934-3940 (1994).
- J. Travis, "Proteins and Organic Solvents Make an Eye-Opening Mix", Science, 262, p. 1374 (1993).
- J. Uhl et al., "Secretion of Human Monocyte Mature IL-1 β : Optimization of Culture Conditions and Inhibition by ICE Inhibitors", Inflammation Res., 44, pp. S211-S212 (1995).
- P. Warner, et al., "PYI Idone HLE Inhibitors: Variation of the 3 and 5 Substituents", Royal Soc. Chem. Abs. (7th RSC-SCI Med. Chem. Symp.), P23 (1993).
- S. Weiner et al., "A New Force Field for Molecular Mechanical Simulation of Nucleic Acids and Proteins", J. Am. Chem. Soc., 106, pp. 765-784 (1984).
- C. Wong & J. McCammon, "Dynamics and Design of Enzymes and Inhibitors", J. Am. Chem. Soc., 108, pp. 3830-3832 (1986).
- P. Wooley et al., "The Effect of an Interleukin-1 Receptor Antagonist Protein on Type II Collagen-induced Arthritis and Antigen-induced Arthritis in Mice", Arthritis Rheum., 36, pp. 1305-1314 (1993).
- J. Yuan et al., "The C. elegans Cell Death Gene ced-3 Encodes a Protein Similar to Mammalian Interleukin-1 β -Converting Enzyme", Cell, 75, pp. 641-652 (1993).


The above-cited documents are listed on the accompanying Form PTO-1449 (submitted in duplicate). Applicants submitted copies of these documents in United States application 09/430,822 (Filing date October 29, 1999) from which this

application claims priority. Accordingly, pursuant to 37 C.F.R. § 1.98(d) applicants have not provided copies of these documents herewith.

Applicants respectfully request that the above-cited documents be (1) fully considered by the Examiner during the course of the examination of this application and (2) printed on any patent issuing from this application. Applicants also request that a copy of the enclosed Form PTO-1449 duly initialed by the Examiner be forwarded to the undersigned with the next communication.

This Statement is submitted more than three months from the application filing date, but before the mailing date of the first Office Action. In accordance with 37 C.F.R. § 1.97, submission of this Statement requires no fee. However, if for any reason a fee is due, the Director is hereby authorized to charge payment of any fees required in connection with this Information Disclosure Statement to Deposit Account No. 06-1075. A duplicate copy of this letter is transmitted herewith.

Respectfully submitted,



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